This election is made **with traverse**.

In the event that this species election is found to be non-responsive, Applicants provisionally elect with traverse the species represented by SEQ ID NO: 37 (pending claim 36). Claims 20-36 and 37-38 read on the elected species. This provisional election is made **with traverse**.

Prior to examination, please amend the above-identified application as follows:

In the Claims:

Please add the following new claims as follows.

--38. The EPOR analog protein according to claim 20 comprising an amino acid sequence that has at least one amino acid substitution as compared to the wild-type EPOR sequence, wherein said substitution is selected from amino acids residues in domains D1 and D2 of said EPOR analog protein.

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REMARKS

Claims 20-38 are pending in this application. Support for new claim 38 is found in pending claim 20. Support for new claim 39 is found in the specification at page page 66, lines 5-6. An Appendix of Pending Claims is attached for the Examiner's convenience.

TRAVERSAL OF SPECIES ELECTION REQUIREMENT:

Applicants submit that the disclosed variant EPOR proteins with specific amino acid changes in various regions should not be subjected to an election of species requirement. If the search and examination of an entire application can be made without serious burden, it must be examined on its merits even though it includes claims to independent or distinct inventions. (MPEP § 803).

The Examiner has pointed out that Claims 21-37 claim distinct polymorphisms of EPOR. Further, the Examiner has asserted that each of these nucleic acid sequences is considered to be structurally independent and distinct because each has a unique sequence.

Applicants respectfully submit that the Examiner has overlooked the underlying concept of PDA™ technology, the computational method by which the invention is generated (See U.S. Pat. Nos. 6,188,965; 6,269,312; 6,403,312 and PCT/US98/07254 and PCT/US01/40091).

PDA™ technology is a computational modeling system that allows the generation of stable proteins. This computational processing results in a set of optimized protein sequences, with desired properties, i.e. capability of binding naturally occurring ligands. (see Specification at page 3, lines 22-25 and page 10, lines 21-24.)

Applicants' method underlying the present invention finds optimized *sequences* in their optimal conformations from among many sequences, not optimal *structures alone* (emphasis added). This method may analyze many amino acids at a defined position or many positions. The present invention claims novel, non-naturally occurring EPOR protein sequences generated by analyzing the interaction of each rotamer with other rotamers and between pairs of potential rotamers, as well as with that of a protein backbone structure. These interactions are then processed to generate a set of optimized sequences that then may be used to generate other related optimized sequences.

Generally, optimization of EPOR protein sequences, using PDA™ technology starts by selecting a known three-dimensional structure of a protein (wild type, non-naturally occurring or variant EPOR protein). This structure for which variable positions are identified is input into a computer. For each variable position or region, amino acid

residues or a set of amino acid side chains or rotamers are chosen. For amino acid side chains or rotamers, those with at least one variable residue position having rotamers from at least two different amino acid side chains may be chosen.

The PDA™ technology calculation uses the energy of interaction of a rotamer or amino acid residue with both the template structure (e.g. backbone structure or any fixed residues) with all possible rotamers the variable positions is calculated. This is done using any number of scoring functions well known in the art. One may vary one position or all possible positions.

For example, the calculation of the energy of interaction may be facilitated by the use of Dead End Elimination (DEE). DEE is used to decrease the number of required calculations by eliminating rotamers that cannot be part of a global minimum. Once the global minimum is reached local minima can be found by using additional analysis, such as Monte Carlo analysis, among others, which makes random changes and recalculates the energy of interaction. This may be an iterative process starting with any known three-dimensional structure, i.e. the wild type protein or non-naturally occurring or a variant protein and obtaining additional non-naturally occurring or variant proteins, which may be made and tested to confirm the resulting proteins have the desired properties.

The PDA™ technology method avoids problems and limitations associated with other protein design strategies by allowing exploration of all sequence space, while avoiding the necessity of actually synthesizing all possible variant proteins to determine whether the resulting variant possesses activity and desired properties. Additionally, a user of PDA™ technology can generate a threshold or cutoff to eliminate disfavored sequences, i.e. those that lack desired biological features, thereby increasing the percentage of useful variants that are synthesized.

As may be seen by the foregoing discussion, the claims are directed to variant EPOR proteins that share common structural (i.e., similar protein structures) and functional properties of EPOR proteins. Accordingly, application of the restriction requirement under 35 USC §121 and 37 CFR 1.141 is inappropriate. Applicants respectfully request reconsideration and withdrawal of the restriction requirement.

Alternatively, if the Examiner does not withdraw the species election requirement, Applicants provisionally elect with traverse, EPOR variants of the D1 and D2 domains of the EPOR protein (new claim 38).

If a single species is required, Applicants elect the species represented by SEQ ID NO: 37, with traverse.

Applicants make this election with the understanding that should allowable subject matter be found, applicants are entitled to consideration of a generic claim encompassing additional species, such as those disclosed in claims 20-38.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Dated: 10/9/02

Respectfully submitted,

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Appendix of Pending Claims

20. An erythropoietin receptor (EPOR) analog protein comprising an amino acid sequence that has at least one amino acid substitution as compared to the wild-type EPOR sequence, wherein said substitutions are selected from amino acids residues comprising one or more of the following regions:

a) the inter-monomer interface;

b) domain D1;

c) domain D2;

d) the conserved WSXWS box (SEQ ID NO:30); and

e) the N-terminal helix.

21. The EPOR analog protein according to claim 20 comprising at least one amino acid substitution from said inter-monomer interface, said substitutions comprising amino acid residues at positions 155, 175 and 178.

22. The EPOR analog protein according to claim 20 comprising at least one amino acid substitution from said inter-monomer interface, said substitutions comprising amino acid residues at positions 133 and 135.

23. The EPOR analog protein according to claim 20 comprising at least one amino acid substitution from said domain D1, said substitutions comprising amino acid residues at positions 40, 53, 55, 57, 69,79,81,85, 96, 98, 100, and 109.

24. The EPOR analog protein according to claim 23 wherein said substitutions are selected from the group of substitutions consisting of W40F, W40Y, Y53F, F55I, Y57F, L69I, V79I, L96F, V100L, and Y109F.

25. The EPOR analog protein according to claim 20 comprising at least one amino acid substitution from said domain D2, said substitutions comprising amino acid residues at positions 120, 121, 127, 129, 138, 140, 142, 156, 158, 160, 174, 183, 192, 194, 196, 198, 207, and 218.

26. The EPOR analog protein according to claim 25 wherein said substitutions are selected from the group of substitutions consisting of L127I, A129V, V138I, L140I, Y156F, Y156W, V158L, V158I, V160I, I174L, Y192I, Y192F, F194I, F194V, F194L, G207W, G207I, G207M, F208I, F208Y, F208E, L218F, and L218I.

27. The EPOR analog protein according to claim 20 comprising at least one amino acid substitution from said WSXWS box (SEQ ID NO:30), said substitutions comprising amino acid residues at positions 209, 210, 211, 212, and 213.

28. The EPOR analog protein according to claim 27 wherein said substitution is A211Y.

29. The EPOR analog protein according to claim 20 comprising at least one amino acid substitution from said N-terminal helix region, said substitutions comprising amino acid residues at positions 11, 15, 17, 18, 19, 29, 37, and 39.

30. The EPOR analog protein according to claim 29 wherein said substitutions are selected from the group of substitutions consisting of K11L, K11W, K11Y, K11A, K11Q, A15L, A15Y, A15M, A15S, A15R, L17F, L17Y, L17I, L17W, L17M, L17K, L18Y, L18N, A19W, A19V, A19Y, A19D, F29L, F29Y, F29R, C37I, C37L, C37E, C37Q, and C37E.

31. The EPOR analog protein according to claim 20 comprising at least one amino acid substitution from said domain D1 and said domain D2, said substitutions comprising amino acid residues at positions 40, 53, 55, 57, 69,79,81,85, 96, 98, 100, 109, 127, 129, 138, 140, 142, 156, 158, 160, 174, 183, 192, 194, 196, 198, 207, and 218.

32. The EPOR analog protein according to claim 31 wherein said substitutions are selected from the group of substitutions consisting of W40F, W40Y, Y53F, F55I, Y57F, L69I, V79I, L96F, V100L, Y109F, L127I, A129V, V138I, L140I, Y156F, Y156W, V158L, V158I, V160I, I174L, Y192I, Y192F, F194I, F194V, F194L, G207W, G207I, G207M, F208I, F208Y, F208E, L218F, and L218I.

33. The EPOR analog protein according to claim 32 wherein the protein comprises SEQ ID NO: 6.

34. The EPOR analog protein according to claim 31 further comprising a linker.

35. The EPOR analog protein according to claim 34 further comprising a dimerization motif.

36. The EPOR analog protein according to claim 35 wherein the protein comprises SEQ ID NO: 37.

37. A receptor analog protein comprising an amino acid sequence that has at least 10 to 24 amino acid substitutions as compared to the corresponding wild-type receptor protein, wherein said receptor analog protein binds a natural ligand for said naturally occurring wild-type receptor protein at the same or higher affinity than said naturally occurring wild-type protein.

38. The EPOR analog protein according to claim 20 comprising an amino acid sequence that has at least one amino acid substitution as compared to the wild-type EPOR sequence, wherein said substitution is selected from amino acids residues in domains D1 and D2 of said EPOR analog protein.